PHOTOREJUVENATION WITH INTENSE PULSED LIGHT: RESULTS OF A MULTI-CENTER STUDY -

NEIL S SADICK MD 1, ROBERT WEISS MD 2, SUZANNE KILMER MD 3, PATRICK BITTER MD 4

1. WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY - 2. JOHNs HOPKINS UNIVERSITY
3. UNIVERSITY OF CALIFORNIA AT DAVIS - 4. STANFORD UNIVERSITY

Abstract

This multi-center study evaluating the role of Intense Pulsed Light (IPL) in the non-ablative rejuvenation of Type I and Type II photoaged skin study was conducted in order to evaluate the clinical efficacy and safety of using IPL in treating clinical. indications associated with photoaged skin. Ninety-three patients of Fitzpatrick skin phenotypes I-III, Fitzpatrick Wrinkle Classes I-II, and Elastosis Scores 1-6 were enrolled in the study. Up to five treatments were performed at 4-week intervals with follow-up visits at 4 and 6 months after the last treatment. Patients received full-face treatments using the recommended parameters. of the Quantum SR/HR (Lumenis Ltd.) with the 560 or 640 rim cutoff filter. Parameters of elastometry, physicians' evaluation of the Elastosis Score ('W/ES'), and global improvement as well as patient satisfaction were analyzed. Results showed that the average Fitzpatrick W/ES improved significantly ($p<0.001$) by 1.39 and 1.32 units at the 4 and 6 months follow-ups, respectively; an improved W/ES evaluation was recorded for 82% and 75% of the patients at each of these time points. In conclusion, IPL treatment is an effective non-invasive, non-ablative method for rejuvenating photoaged skin vith minimal adverse events, no downtime, excellent long-term results, and a very high measure of patient satisfaction.

Introduction

The visible appearance of photoaged skin is characterized by dermal and epidermal structural changes, coarse skin texture, wrinkling, pigmentation alterations, telangiectasias, and epidermal malignancies, as well as actinic kerastoses in some cases. Non-ablative photorejuvenation. improves the texture and overall appearance of photoaged skin without causing thermal destruction and regrowth of the epidermis and superficial dermis, as is the case with ablative procedures. One such non-ablative skin rejuvenation technique involves Intense Pulsed Light (IPL), which enables fulI face, neck, chest, and arm rejuvenation by means of a broadband noncoherent light source, which ranges from 560 to 1200 nm. The wide wavelength range of IPL provides the added benefit of being able to target different skin structures, allowing for comprehensive cosmetic improvement of the skin's appearance and texture. This benefit is achieved with minimal side effects and no patient down- time due to the characteristics of IPL and the separation of the treatment into multiple sessions. Notably, the efficacy of IPL in the treatment of benign vascular and pigmented lesions, including those manifested in photoaged skin, has been previously documented. In recent years, several small scale studies have expanded its reported effect to amelioration of rhytids and elastosis as well. The present study outlines the, results of a larger multi-center study, intended to document the possible benefits and side effect profiles associated with IPL treatment of early Type 1 and Type II photoaged skin (Table 1).

Table I: Classification of Photoaged Skin

Type I	Epidermal – superficial dermal
	Vascular – redness, telangiectasia
	Pigmentary – mottled dyschromia, lentigos, and ephelides
Type II	Mid deep dermal
	Rhytides
Type III	Subcutaneous musculoskeletal
	Lipodystrophy – contour irregularities
	Muscle atrophy
	Bone atrophy

The study group consisted of 84 females and 9 males aged 30 to 77 years (mean 49.2 ± 8.9). To be considered eligible, patients had to be of Fitzpatrick skin type 1 (3 patients), type II (50 patients), type III (40 patients or type IV (none) and of Fitzpatrick 4 Wrinkle Class I-II/Elastosis Score (W/ES) 16 (Figure 1, Table 2). Ninety-two of the 93 enrolled patients were presented with clinical indications associated with type II photorejuvenation (wrinkles and elastosis); approximately 65% of these patients were also presented with type I indications (benign vascular and pigmented lesions).

Figures 1-1A through 1-9 B: Fitzpatrick Classification of Wrinkling and Degree of Elastosis used in Multi-Center Study.

Mild Elastosis (1-3): Fine textural changes with subtly accentuated skin lines.

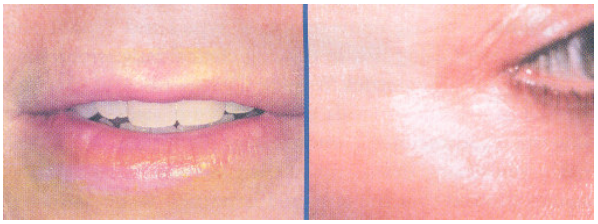


Fig. 1-1 A Fig. 1-1 B

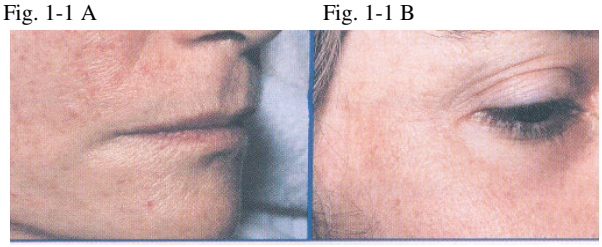


Fig. 1-2 A Fig.1-2 B

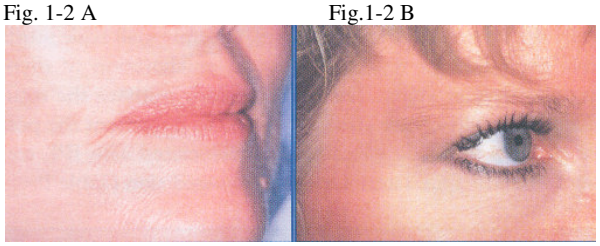


Fig. 1-3 A Fig. 1-3 B

Moderate Elastosis (4-6): Distinct popular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia.

Fig. 1-4 A Fig. 1-4 B

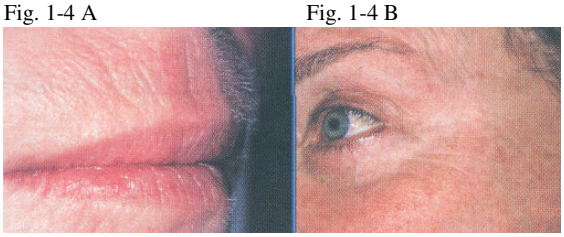


Fig. 1-5 A Fig. 1-5 B

Fig. 1-6 A Fig. 1-6 B

Severe Elastosis (7-9): Multipapular and confluent elastosis (thicke ned yellow and pallid) approaching or consistent with cutis rhomboidalis.

Fig. 1-7 A Fig. 1-7 B

Fig. 1-8 A Fig. 1-8 B

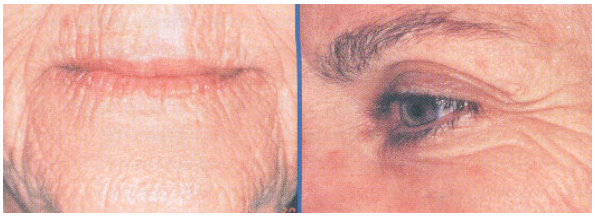


Fig. 1-9 A Fig. 1-9 B

Table II: W/ES distribution

	Total	%
W/ES 1	5	5%
W/ES 2	2	2%
W/ES 3	12	13%
W/ES 4	38	41%
W/ES 5	16	17%
W/ES 6	19	21%
Grand Total	92	100.0%

Up to five full-faced treatments were performed at 4-week intervals. Four patients discontinued from the study due to personal reasons after having received only one treatment, and thus are not included in the results analysis. Follow-up visits were scheduled for all patients at four and six months after the last treatment. Treatments were performed with the Quantum SR/HR (Lumenis Ltd- Yokneam, Israel) using the 560 nm or 640 nm cutoff filters at a single, double, or triple pulse mode with fluences of 20-44j/cm², 2-7 ms pulse duration, and 10-70 ms inter-pulse delay. At each treatment, single or multiple passes were performed.

Prior to cach treatment and at both follow-ups, the patients face was photographed using a Nikon N70 camera (Nikon Inc., Melville, NY, USA) and a Canfield Stereotactic face device (for positioning the camera relative to the patient; Canfield Scientific, Inc- Fairfield, NY, USA). Special care was given to ensure proper and reproducible lighting conditions and centralized film processing.

Thirty minutes prior to treatment, the subject's face was thoroughly cleaned and 1/4 inch thick layer of ELA-Max, topical anesthetic cream (now available as L-M-X-4, Ferndale Laboratories Inc- Ferndale, MI, USA) was applied for pain management. The cream was then removed and the face was cleaned before the procedure itself. Patients were placed in a supine position and cold BVL coupling gel (Eco-Med Pharmaceuticals Inc- Mississauga, Ontario, Canada) was applied to the skin. The light guide was placed over the gelled area, with the crystal tip immersed in the gel (approximately 1-2 min above the skin). Light was only emitted after eye protection was set in place and the patients eyebrows were covered with moist gauze pads.

Prior to each treatment and at the follow-up visits, the investigators recorded the patient's full face Fitzpatrick W/ES; beginning from the second treatment visit, they also recorded their assessment of the overall improvement in the patient's facial appearance using a 5-point percentage scale: 'No improvement', '0-25% improvement', '25-50% improvemment', '50-75% improvement', '75-100% improvement'. At both follow-up sessions, the patients also filled out a questionnaire pertaining to their assessment of overall cosmetic improvement (using the same 5-point percentage scale) and to their level of satisfaction with the treatment results (using a 5-point satisfaction seale: 'Most satisfied', 'Satisfied', 'Indifferent', 'Not satisfied', 'Disappointed').

Non-invasive measurements of facial skin elasticity were conducted at the scientific site (Sadick) using the Cutometer, SEM 575 (Courage & Khazaka Electronic GmbH, Cologne, Germany). The Cutometer is an established research tool in the field of clinical dermatology. Briefly, this device is comprised of a probe tip through which pre-determined negative pressure is applied to the skin for set durations. The resulting skin deformation provides information regarding the skins laxity, stiffhess, and elasticity. These elasticity measurements were performed at the pre-treatment visit and at the four- and six-montli follow-up visits. A11 measurements were carried out by the same person in an air-conditioned roem (temperature ~20ºC, air humidity ~60%). Using 'mode V of the Cutometer, negative pressure of 450-500 mbars was applied to the skin for 1-5 seconds, followed by 1-5 seconds of relaxation. The resulting skin defórmation was recorded via computer and analyzed using the Cutometer software for Microsoft Windows (version 9.2.0.0).

Table III: Investigator Evaluations

W/ES Distribution at each time point

Time Point	Mean W/ES ± S.D.	Mean W/ES Improvement	Sample Size	P-value
Pre treatment	4.45 ± 1.05	–	85	–
4 weeks FU	3.98 ± 1.43	0.47	85	p<0.001
8 weeks FU	3.89 ± 1.17	0.55	85	p<0.001
12 weeks FU	3.64 ± 1.95	0.81	84	p<0.001
16 weeks FU	3.42 ± 1.04	1.08	78	p<0.001
4 months FU	3.13 ± 1.02	1.39	72	p<0.001
6 months FU	3.19 ± 1.10	1.32	75	p<0.001

RESULTS

Statistically significant improvement in the average Fitzpatrick W/ES evaluation was recorded following IPL treatment (Table III). The W/ES improved from 4.45 pre-treatment to 3.13 and 3.19 at four and six months post-treatment, respectively Overall, an average improvement greater than one W/ES unit

was recorded, e.g., reduction of 1.39 and 1.32 at each of the follow-ups. Notably this improvement was shown to be statistically significant ($p<0.001$, t-test for paired data). The total percentage of patients with an improved W/ES reached 82% and 75% at four and six months post-treatment respectively (Table IV).

The physicians: assessment of the patients' wrinkle condition was supported by the objective scientific measurement of skin elasticity, which showed a statistically significant overall mean increase of 15% in the patients: skin elasticity at six months post-treatment ($p<0.01$, Wilcoxon for paired data). The biologically meaningful ratios of the parameters provided by the Cutometer include: R2 (Ua/Uf - the ratio between the maximum amplitude and the re-deformation ability of the skin (gross elasticity); R5 (Ur/Ue) - the ratio of the immediate retraction and the immediate deformation (net elasticity); and R7 (Ur/Uf) - the ratio between the immediate retraction and the total deformation (biological elasticity). The last is not reported in Table 7 since it closely parallels R5 (Ur/Ue), which is considered the variable of choice for quantifying skin aging independently from skin thickness' (Table V).

Table IV: Integrated W/ES Change Status

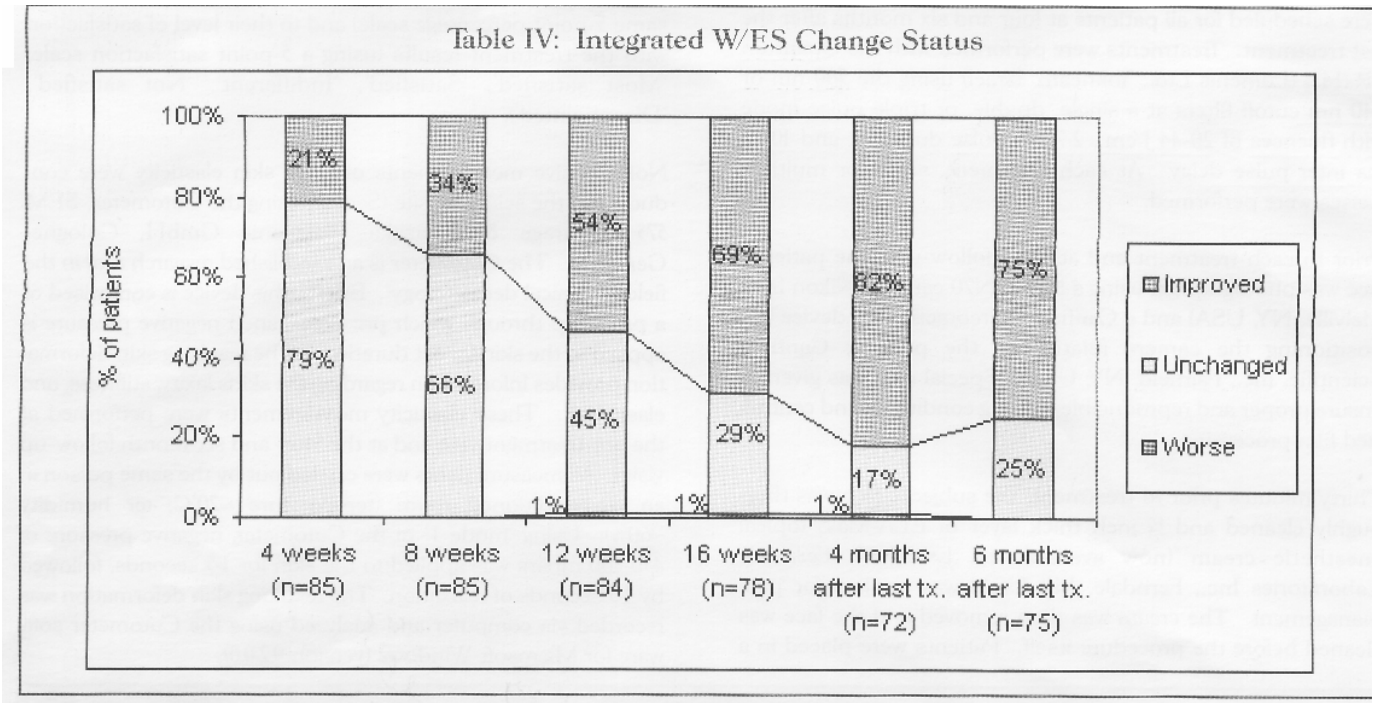


Table V
Skin Elasticity – Cutometry Measurements and Their Comparison between Time Points

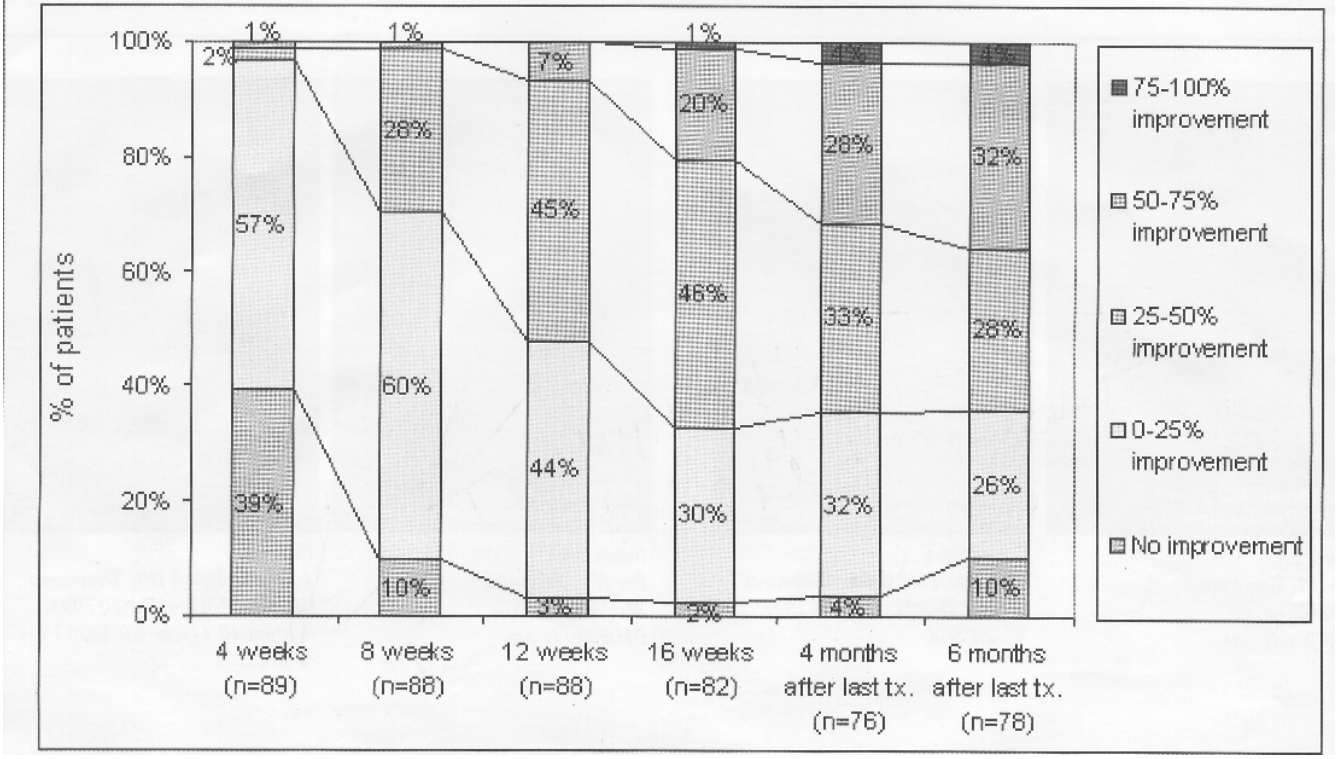
	Pre Tx	4 months FU	6 months FU	4 months FU vs. pre tx	5 months FU vs. pre tx
Sample size	21	9	18	7	16
Gross Skin Elasticity; R2 (Ua/Uf)	0.619	0.702	0.727	0.053	0.144
Net Skin Elasticity; R5 (Ur/Ue)	0.544	0.661	0.648	0.068	0.152
Average change in skin elasticity				6.05%	14.77%
p-value				p>0.05	p<0.01

Significant improvement was also seen using the investigators, assessment of overall improvement in facial appearance, which reflected pigmentary, vascular, and observed dermal structural change, ie., rhytid reduction. The first IPL treatment was able to trigger improvement of overall appearance in 61% of the study population. The number of patients showing improvement continued to increase as the study

treatments progressed, reaching 98% by the fifth treatment, and remained fairly steady with 96% and 90% at four and six months after the last treatment respectively (Table VI). A similarly impressive percentage of patients reported having improvement in their overall appearance at four and six month post-treatment, respectively (Table VII). The increase in both the physicians' and patients' assessment of overall improvement were shown to be statistically significant ($p<0.001$, t-test for paired data). Notably, no significant differences were found between the assessments provided by the patients and the physicians. Representative photographs of patients treated in the study are shown in Figures 2 through 5.

Table VI: Improvement Scale Analysis (Physician Assessment)

Distribution of Percent Overall Improvement Appearance
by Study Time Point, evaluated by the investigator



The majority of patients were satisfied with the results of treatment, as indicated by the total combined percentage of 'Satisfied' and 'Most satisfied' patients, ie., 80% and 70% at four and six month post-treatment, respectively (Table VIII).

Out of the 441 treatments that were performed during the study, only 25 (~57%) resulted in minor complications in 20 patients (Table IM. These complications consisted mostly of mild to moderate erythema, edema, purpura, and hyperpigmentation, all of which were resolved within several days to a week without hindering the treatment schedule. The majority of these cases did not require: any form of medical intervention; the prescribed remedial therapy usually consisted only of cold compresses and topical hydrocortisone treatment.

Discussion

The present multi-center study demonstrates that non-ablative treatment with Intense Pulsed Light is safe and effective for the reduction of wrinkles and elastosis, (Type II photoaging) and benign vascular and pigmented lesions (Type I photoaging).

A total of 93 patients with photoaged skin were: treated in a series of four to five full face IPL treatments separated by 4-week intervals. A significant long-term mean reduction greater than 1.3 Fitzpatrick W/ES units was evaluated at four and six months after the last treatment. Over 40% of the

patients presented an average improvement of 2 to 5 W/ES units at these time points. These results were further substantiated by the significant overall mean increase of ~15% in the patients: skin elasticity, as measured via the Cutometer. Significantly, these results were also translated to high patient satisfaction rates.

The overall improvement in the patient's facial appearance was also shown to be statistically significant, with more than 90% of the patients showing visible long-term improvement at the two follow-up visits. Analyses of patient subgroups within the study population (not shown) provided further support to the claim that rapid patient visualization of improvement is appreciated because color hues of photoaged skin show more rapid improvement than that of collagen stimulation- induced rhytid amelioration.

Table VII: Patienfs Change in Appearance
P-value (4 months vs. 6 months)>0.05, t-test paired data

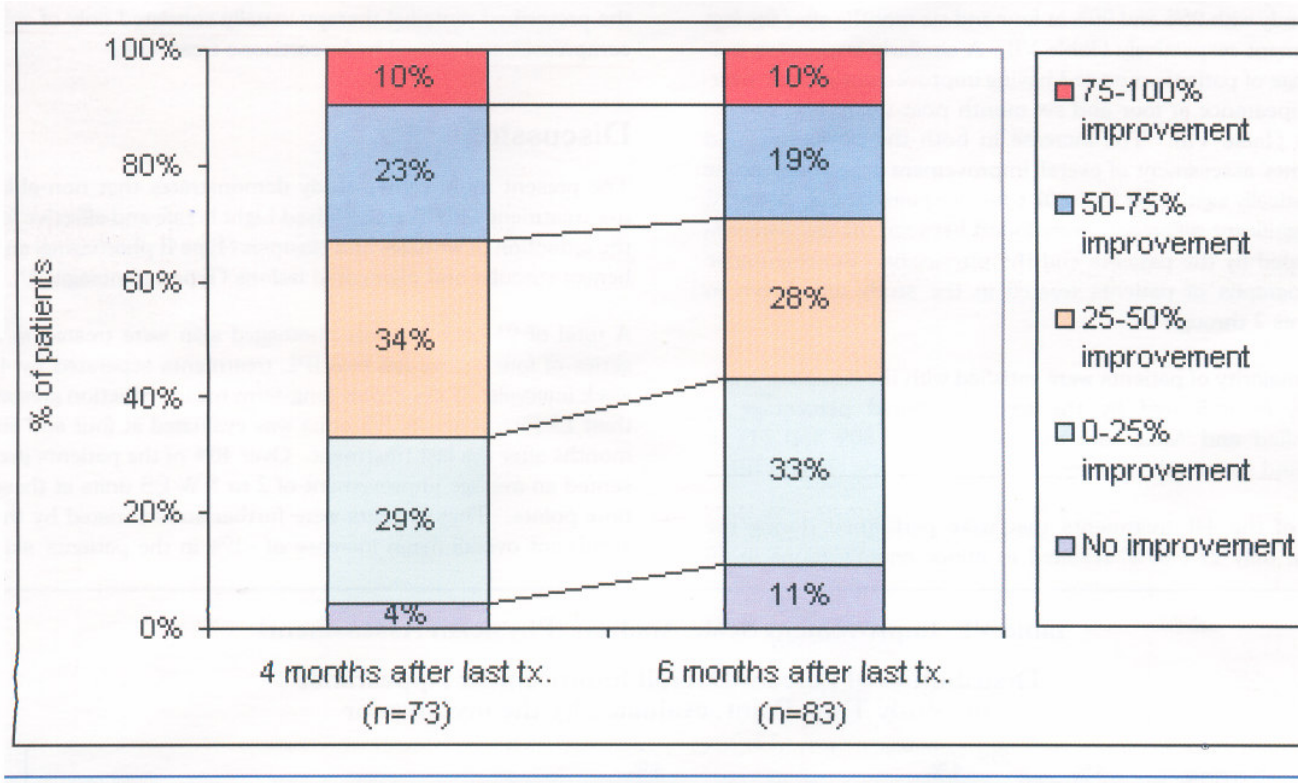


Figure 2A.
Pre-IPL Treatment
W- 2/ES-6
SLK Study Site

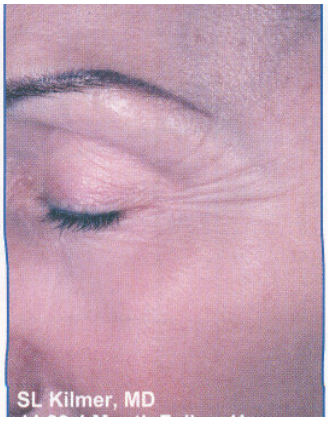


Figure 2B:
4 months post 4 IPL Treatments
(560nm 25-30J/cm² 2.4/4,0 PD.)
W=21ES-4

Figure 3A
Pre-IPL Treatment
W=2/ES=5
PHB Study Site

Figure 3B:
4 months post 5 1PL treatments
(560nm 28-31J/cm² 2.4/4.0 P.D)
(640nrn 40-44J/cm² 6.0/7.0/7.0 P.D)
W=I/ES=2

The treatment protocol utilized in the presented study further supports Bitter's observation that performing a series of multiple treatments allows for a gradual, progressive improvement while enabling treatments to be gentle enough to avoid adverse effects or patient downtime.

The advantages of IPL photorejuvenation when compared to other nonablative technologies include reduced risk of ocular injury as well as minimal patient discomfort. Furthermore, this technology allows for a large spot size and is therefore suited for treatment of larger areas of nonfacial skin, i.e., neck, chest, forearms, hands, and legs.

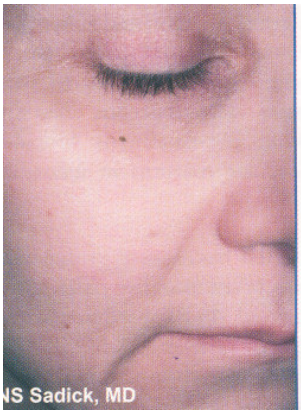


Figure 4A
Pre-IPL treatment
W7=2/ES=4
NSS Study Site

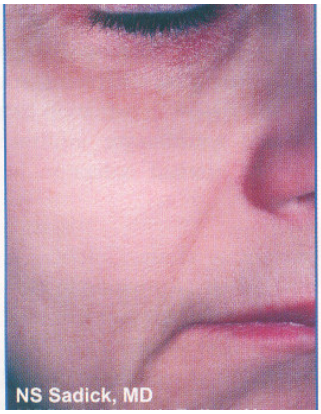


Figure 4B
4 months Post 5 IPL treatrnents
(560nm 32J/cm² 2.4/4.2 PD.)
W=1/ES=2

Figure 5A
Pre-IPL treatment
W=2/ES=4
RAWY Study Site

Figure 5B
1 month Post 4 IPL treatments
(560nm 25-29J/cm² 2.4/4.0 PD.)
W=1/ES=2

Table VIII: Patient's Satisfaction Distribution

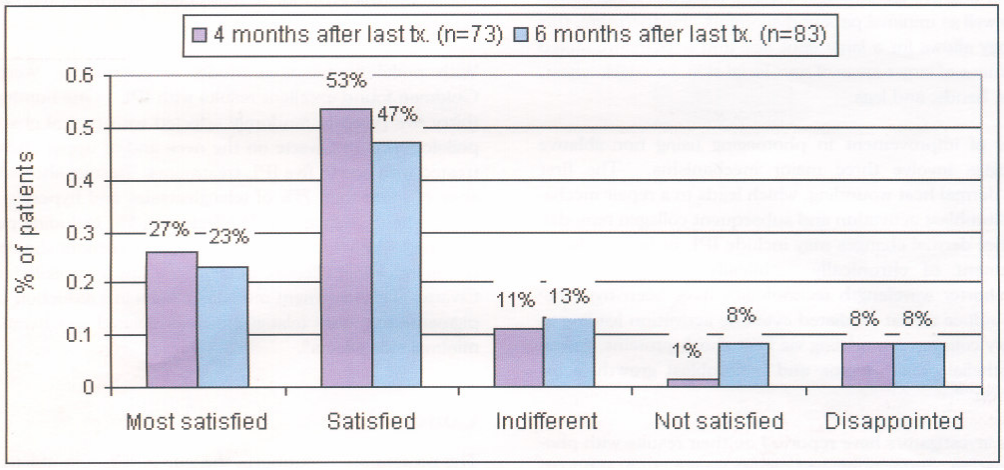
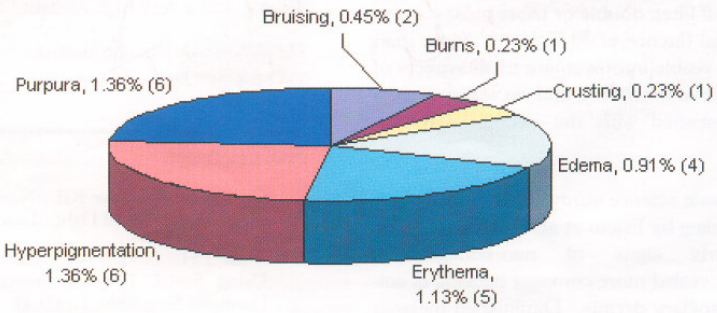


Table IX: Complication profile

The complications occurred in 20 patients, representing 21.5% of the IPL-treated patients



Theories of improvement in photoaging using non-ablative technologies involve three major mechanisms. The first involves dermal heat wounding, which leads to a repair mechanism of fibroblast activation and subsequent collagen remodeling. Other dermal changes may include IPL or laser-induced displacement of chronically actinically- damaged dermis. Finally shorter wavelength technologies have been hypothesized to induce a heat-mediated cytokine activation leading to secondary collagen remodeling via heat shock proteins, vascular endothelial growth factor, and b fibroblast growth factor modulation"".

Previous investigators have reported on their results with photorejuvenation. Bitter published results from a study conducted on 49 patients with various degrees of wrinkling, skin coarseness, irregular pigmentation, increased pore size, and telangiectasias. At least four treatment sessions were performed at 3-4 week intervals. Treatment parameters included a 550 nm or 570 nm cut-off filter, double or triple pulses, pulse duration of 2.4-4.7 ms, and fluence of 30-50 J/cm². More than 90% of patients achieved visible improvement in all aspects of photoaged skin with minimal downtime and no scarring; 88% of the subjects were satisfied with the overall treatment results.

In a recently published basic science study studying the effect of IPL on dermal remodeling by Prieto et al, histopathologic analysis revealed early signs of neo-collagenesis. Ultrastructural analysis revealed more compact packing of collagen fibers within the papillary dermis. Diminished melanin was identified at the dermal- epidermal junction and subepidermal regions. Demodex organisms appeared coagulated in immediate posttreatment specimens while organisms were mostly absent in follow-up biopsies. Pilosebaceous units displaying lymphocyte infiltrates in pretreatment biopsies showed marked reduction in cellular reaction in follow-up ones.

In another study, Goldberg reported histological evidence of new collagen formation in biopsies taken from five patients six months following four IPL treatments". In a subsequent study, Goldberg et al., using a 645 nm cut-off filter and 40-50J/cm² fluences, found qualitative photographic improvement in 25 of 30 patients after four treatment sessions".

In two subsequent studies, Negishi et al. treated 73 and 97 photoaged Asian patients with IPL. The cut-off filters utilized in the later study (97 patients) were 550 and 570 nm for three to six treatments at 2-3 week intervals. Good to excellent results were achieved in more than 90% of the patients for pigmentation, more than 83% for telangiectasia, and more than 65% for skin texture.

With poikiloderma as a model of photoaging, Weiss and Goldman found excellent results with IPL. One hundred and thirty-five patients randomly selected with typical changes of poikiloderma of Civatte on the neck and/or upper chest were treated with one to five IPL treatments. Results showed clearance of more than 75% of telangiectasias and hyperpigmentation. The incidence of side effects was 5%, including pigment changes". In a subsequent study, these authors showed that IPL is indeed an effective mode of therapy for poikiloderma of Civatte. This treatment modality results in a reduction of both pigmentation and telangiectasia- associated erythema, with minimal side effects.

Conclusion

The present study supports the role of IPL non-ablative rejuvenation in the treatment of vascular, pigmentary, and dermal elastotic alterations associated with photoaged skin. IPL is an effective non-invasive method for rejuvenating photoaged skin with minimal adverse events, no downtime, excellent long-term results, and a very high measure of patient satisfaction.